

REMARKS

Applicants respectfully request that the claims be reconsidered for allowance in view of the present remarks.

I. Status of the Claims

Claims 1-5, 7, and 8 are pending in the instant application. Claim 4 is subject to objection as depending from a rejected claim. Claims 1-3, 5, 7, and 8 stand rejected under 35 U.S.C. § 112 first paragraph as allegedly not being enabled by the specification as filed. Applicants respectfully traverse the rejections and request reconsideration in light of the above amendments and the following remarks.

II. Priority Claim

The Examiner acknowledged the claim to the benefit of U.S. Provisional Application No. 60/203,162, filed May 9, 2000 but noted that Applicants were not granted priority for the amino acid sequence of SEQ ID NO:77. Applicants submit that the Examiner has not identified intervening art (*i.e.*, art having an effective date later than the actual filing date of the above-identified provisional application, and prior to the actual filing date of the instant application). Accordingly, the Examiner's statements regarding the validity of the priority with respect to SEQ ID NO:77 unnecessarily contribute to a confusion in the record and Applicants request withdrawal of the statements relating to priority in order to clarify the record.

III. Rejection under 35 U.S.C. §112, first paragraph, for lack of enablement should be withdrawn

Claims 1-3, 5, 7 and 8 were rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner, while the specification is enabling for a caspase polypeptide comprising the amino acid sequence of SEQ ID NO:77, the specification assertedly does not provide enablement for any caspase polypeptide comprising an amino

acid sequence being at least 98%, 95% or 90% homologous to a sequence of SEQ ID NO:77, wherein said polypeptide comprises a QACXG domain and possesses caspase catalytic activity. Applicants request reconsideration of the rejection in view of the remarks presented herein.

In supporting the rejection, the Examiner states that the "specification does not **sufficiently** establish (A) regions of the protein structure which may be modified without effecting caspase activity; (B) the general tolerance of caspases to modification and extent of such tolerance; (c) a rational and predictable scheme for modifying any amino acid residue of any caspase variant of SEQ ID NO:77, with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful." Applicants respectfully disagree with the Examiner.

The claims of the present invention are directed to a caspase protein and variants thereof that are at least 90% homologous to the full-length sequence of SEQ ID NO:77. However, the claims also specify that such variants must possess caspase activity **and** the claims specify that the variants must possess a domain that contains the sequence QACXG. The disclosure in the specification is not directed solely to SEQ ID NO:77, it provides a teaching of a numerous variants of this sequence, all of which are novel caspases.

Caspases are a class of proteins that were well characterized by those of skill in the art at the time the instant application was filed. For example, as can be seen at page 1, lines 11-17 of the specification, numerous mammalian caspases had been identified. Those of skill in the art are aware that mature active caspases are made of four subunits (two small and two large) and that residues from both subunits contribute to substrate binding pockets of caspases and that there is a "***highly conserved pentapeptide (QACXG) containing the catalytic cysteine, present in the large subunit.***" *Id.* The present invention identifies a previously unknown caspase, i.e., ***caspase 12.***

In Figure 2 of the specification there is provided a sequence alignment of eleven different isoforms of caspase 12, including the sequence of the non-naturally occurring variant of the human caspase 12 isoform that having the sequence set forth in SEQ

ID NO:77 and that is embraced by the instant claims. Figure 3 shows an alignment of SEQ ID NO:77 with the sequence of murine caspase 12. Figure 4 details the alignment of SEQ ID NO:77 with murine caspase-12, human caspase-1, human caspase-4, human caspase-5, human caspase-6, human caspase-7, human caspase-8, human caspase-9, human caspase-10, human caspase-13, and human caspase-14. Figure 5 shows the alignment of SEQ ID NO:77 with human caspases-4, -5, -13 and -1.

Referring to the sequence alignment in Figure 3, the residues that are conserved between SEQ ID NO:77 and the murine caspase-12 are clearly depicted. The CARD domain, the ICE-p20 domain, the ICE-p10 domain and the active site amino acid residues also are clearly indicated, and the specification teaches the residues of the active site need for activity. Similarly, the sequence alignment data shown in Figure 4 (*i.e.*, the alignment between SEQ ID NO:77 and other human caspases) specifically identify active site residues as residues that are identical in all of the caspases depicted; the figure further reveals conservative substitutions and residues that may be considered as allowable substitutions. Figure 5, which is a sequence alignment among SEQ ID NO:77 and the mostly closely related caspases other than caspase-12 caspase provides even more guidance as to those residues that are conserved and those residues that are not conserved between the various caspases, and further delineates which residues are found in the CARD domain, in the ICE-P20 domain, in the ICE-P10 domain, and in the active site.

Figures 1-5 therefore provide explicit detail of sequences that are conserved and sequences that are varied among various caspases as compared to SEQ ID NO:77. One of skill in the art seeking to produce a variant of SEQ ID NO:77 that has 90% homology would review these figures and observe which residues may be modified and which should be conserved. This information along with the fact that the sought-after variants must contain at least the QACXG catalytic domain and must possess caspase activity, provides ample guidance to produce a variant within the scope of the claims of the present invention.

As of the May 9, 2000 priority date of the instant application, one of skill in the art was in full possession of the techniques required to produce a protein having 373 amino acids. Further, methods for the production of variants of a known sequence, using site-specific mutagenesis, *etc.*, were well known and the Examiner acknowledges that fact.

Testing the variants for caspase activity was also disclosed in the specification, which teaches an enzymatic assay for assessing the activity of recombinant human caspase-12 (see, *e.g.*, specification, page 107, lines 9-21). Additionally, the specification expressly teaches one of skill in the art how to determine whether a caspase can serve as a substrate for calpain, an enzyme known to activate murine caspase-12 (see specification page 112, line 20 to page 114, line 5). Thus, the skilled artisan would know how to make a protein of the invention and the specification demonstrates how to determine the activity of such a protein. The description of these assays and results shows one of skill in the art how to determine whether a given protein possesses caspase-specific, proteolytic activity. Finally, Applicants disagree with the Examiner's effective assertion that the claim embraces an "infinite" number of proteins. the claims as amended define the polypeptides of the invention in terms of a structure that is 90% identical to SEQ ID NO:77 at the amino acid level and define the inventive polypeptides functionally in terms of caspase activity. The class of such polypeptides does not even approach an infinite number of proteins. Hence, the specification provides enabling support of a scope commensurate to the scope of the claims.

Given the explicit recitation of amino acid residues of caspases that may be conserved and the amino acid residues that form a part of various domains of caspases as recited in Figures 1-5, Applicants respectfully disagree with the Examiner that the application fails to provide guidance as to which regions may be modified without affecting caspase activity. The skilled artisan would modify those sequences that are non-conserved and are not involved in the catalytic domain of caspases as shown in the Figures of the specification.

Moreover, the specification expressly demonstrates that the CARD region of caspase 12 may be removed, with the resultant protein retaining caspase activity (see specification page 109, line 15, through page 110, line 7; Figure 9). These teaching of the activity of the variant lacking a CARD domain in the specification provides but one example of the requested support for the "general tolerance of the claimed caspase to modification and extent of such tolerance."

In view of the preceding remarks, Applicants submit that the skilled artisan could readily make and use a protein as claimed in the present application. As such, the

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Applicants respectfully request withdrawal of the rejection under §112, first paragraph, and reconsideration of the claims.

IV. Conclusions

Applicants believe that all of the rejections have been overcome and the claims of the instant application are now in condition for allowance and request an early indication of such a favorable disposition of the case. The Examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

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Respectfully submitted,

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